DOES FULL ENTERAL FEED FROM DAY ONE OF LIFE INFLUENCE WEIGHT GAIN IN HEMODYNAMICALLY STABLE VLBW BABIES WEIGHING BETWEEN 1000-1500 GRAMS AS AGAINST STANDARD FEEDING? - AN OPEN LABEL RANDOMISED CONTROL TRIAL

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

DM (NEONATOLOGY)

2011-2014

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2014

CERTIFICATE

This is to certify that the dissertation entitled **"Does full enteral feed from day one of life influence weight gain in hemodynamically stable VLBW babies weighing between 1000-1500 grams as against standard feeding? - An Open Label Randomised Control Trial"** is a bonafide work done by **Dr.S.Ramya** under my guidance and supervision during the period between December 2013 – March 2014 towards the partial fulfillment of requirement for the award of **D.M. (Neonatology)** degree examination to be held in August 2014 by The Tamilnadu Dr.M.G.R. Medical University, Chennai.

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This is to certify that the dissertation entitled **"Does full enteral feed from day one of life influence weight gain in hemodynamically stable VLBW babies weighing between 1000-1500 grams as against standard feeding? - An Open Label Randomised Control Trial"** is a bonafide work done by **Dr.S.Ramya, Madras Medical College** in partial fulfillment of the university rules and regulation for award of D.M.(Neonatology) under my guidance and supervision during the academic year (2014)

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DECLARATION

I solemnly declare that this study title **"Does full enteral feed from day one of life influence weight gain in hemodynamically stable VLBW babies weighing between 1000-1500 grams as against standard feeding? - An Open Label Randomised Control Trial"** was my original work in the Department of Neonatology, Institute of Child Health and Hospital for Children, Egmore, Chennai under the guidance and supervision of **Prof.Dr.J.Kumutha, MD., DCH.,** Professor & Head of the department , Department of Neonatology, Madras Medical College , Chennai. This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of **D.M. (Neonatology)**

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr. S. Ramya,

The Institutional Ethics Committe of Madras Medical College reviewed and discussed your application for approval of the proposal entitled **"Does full caloric enteral feed from day 1 of life increase weight gain in hemodyamically stable VLBW babies weighing between 1000-1500 gms as against standard feeding - A Randomised Controlled Trial"** No.32112013

The following members of Ethics Committee were present in the meeting held on 13.11.2013 conducted at Madras Medical College , Chennai – 3 .

1. Dr. G. Sivakumar, MS FICS FAIS	-- Chairperson
2. Prof. R. Nandini, MD Director ,Instt of Pharmacology , MMC , Ch-3	-- Member Secretary
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6. Thiru. S. Govindasamy, BABL	-- Lawyer
7. Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd / Chairman & Other Members

The Institutional Ethics Committee experts to be informed about the progress of the study , and SAE occurring in the course of the study , any change in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

13/11/13

Member Secretary , Ethics Committee

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CONTENTS

INTRODUCTION

Preterm neonate should grow similar to the intrauterine growth of the normal fetus of the same gestational age postnatally[1]. But, most preterm neonates end up in a growth-restricted state during their hospital stay after birth. Currently, postnatal or extra uterine growth failure is a problem in the majority of very low birth weight infants[2].

Studies have shown that inadequate nutrition during vital stages of development results in decreased number of brain cells and dendritic connections, abnormalities in behavioral and cognitive outcomes. The evidence suggests that early nutrition and neurodevelopment is closely linked and we can improve outcomes by preventing "nutritional insults" during the first weeks after birth[2]. Introduction of enteral feeding is delayed in these babies due to the fear of feed related issues and owing to poor nutrition they enter into a catabolic state, which results in growth restriction. There is a critical window of opportunity, between birth and birth weight gain, when optimal nutrition has its greatest benefit [3].

The unique immunological factors present in the human milk outweigh any issues that can crop due to early feeding in VLBW babies. Maternal milk is the ideal diet for these babies. When mother's own milk is not available the next best option is the donor milk, because of the

lower incidence of necrotising enterocolitis, septicemia and better feeding progression with donor milk when compared to the use of formula feed.

International statement

The AAP statement and WHO &UNICEF joint statement indicated that donor breast milk might be a best alternative option for babies whose mothers are not able to provide their own milk.

Synthesized formulas do not provide the non-nutrient components of human milk such as secretory IgA, lysozyme, oligosaccharides, polyunsaturated fatty acids, and platelet-activating factor (PAF)-acetylhydrolase. These non-nutrient components of human milk contribute to GI mucosal integrity, function, and boost immunity against various GI infections.

At present there is no consensus among healthcare professionals on feeding practices in VLBW infants. There are wide variations in feeding practices regarding the initiation and rate of progression of enteral feeds. The heterogencity of feeding practices are individual based rather than evidence based.

In utero a fetus constantly swallows amniotic fluid. The amniotic fluid plays an important role in growth and development of GI tract in

fetal life. Postnatally, enteral feedings also stimulate the motility of the GI tract and various hormonal secretions [4-6].

In VLBW neonates the earlier achievement of full enteral feeding is very important. Full enteral feeding results in decreased risk for sepsis, liver dysfunction, inadequate growth and reduced mineral accretion [7]. Early introduction of enteral feeds is advantageous in resource limited settings where the availability and usage of TPN is limited and severe infection (septicemia, pneumonia) is an important cause of mortality and morbidity.

Hence it is worthwhile to study about achievement of full enteral feeds from day one of life using exclusively human milk. This trial also gives confidence and encouragement for mothers for achieving successful lactation and dispels the disbelief among the health care professionals regarding various perceived limitations about enteral feeding.

REVIEW OF LITERATURE

Growth in preterm

Proper early nutrition of VLBW neonates results in an adequate growth and avoids late unphysiological catch-up growth [8]. Adequate parenteral and enteral nutrition is associated with better outcomes for these infants [9]. The postnatal weight gain of these babies is associated with better neurological outcomes at two years.

The low nutrient intake plays a major role in growth failure [10]. The early parenteral and enteral nutritional support provided is very low compared to the fetal nutrient transfer. This results in significant protein and energy deficits leading to growth restriction of these neonates.

Feeding in very low birth weight neonates

Optimal nutrition during the neonatal period is very important. Early introduction and rapid achievement of full enteral feeding is a priority in the nutritional management of VLBW infants, because it reduces the need for parental nutrition, risk of infection and the duration of hospital stay. In resource limited settings where it is difficult to administer TPN early initiation of breast feeding is very important.

One of the most important goals during the care of VLBW neonates is the attainment of full enteral feeds [11]. In feeding practices of preterm VLBW infants areas of ambiguity, uncertainty and striking unevenness are common rather than standardized evidence based protocols [11].

Feeding practices

The analysis of various reviews finally concluded that trophic feeding, early initiation of feeds and rapid feed advancement ensures less feed intolerance and lesser time to achieve full enteral feeds.

Trophic feeding

Trophic feeding improves gut motility, helps in earlier attainment of full enteral feeding and reduces cholestasis [12-14].

The Cochrane review (2013) of trophic feeding versus enteral fasting for VLBW infants including nine trials with 754 infants involving few babies of extremely preterm, ELBW and growth restricted concluded that there is no significant difference in the time taken to regain birth weight and to establish full enteral feeds[15]. Meta-analyses did not detect statistically significant effects on the incidence of NEC and late-onset infection.

Early introduction of enteral feeding

Early enteral feeding strategies have the potential to affect important outcomes. Hence it is essential to formulate an uniform policy on the best available evidence possible. But at present the feeding protocols are conflicting across Nations and even within the Neonatal units. Initiation of enteral feeding was delayed mostly due to the fear of necrotising enterocolitis but evidence for this practice is weak.

Benefits of early enteral feeding

Early introduction of enteral feeding is linked with better growth and nitrogen balance. It prevents gastro intestinal atrophy, colonisation of enteropathogenic organisms, decreases the need for intravenous fluid and total parenteral nutrition and improves the mucosal immunity. Animals studies have shown that early feeding was associated with improved maturation of gut associated immune function [16].

Newborns babies are lacking in secretory IgA at birth. Maternal colostrum contains high concentrations of IgA helps in the development of innate immunity in the Payer's patches of the small intestine. Human milk contains immunoglobulin of which IgA is 90% and remains consistently high whereas other immunoglobulin decreases over time with lactation [17].

Wang et al [18] did a study among 49 very low birth weight infants to evaluate the safety and benefit of starting enteral feeding early without parenteral nutrition. The neonates were divided into two groups. Group A (1001-1250 gm, mean GA 29 weeks) and Group B (≤1000 gm, mean GA 27weeks) and received either breast milk or premature formula. Groups A babies regained their birth weight at 20 days and group B babies regained at 25 days and there was no increase in the risk of NEC with this feeding strategy.

De Nisi et al [19] did a study in the Centre of Neonatology of Trento, over a period of 16 years (1994-2009) on early enteral exclusive feeding (EEEF) using banked human milk followed by mother milk. Among 308 babies (weight 750-1249 grams and GA > 26 weeks) admitted, 175 babies (59 %) were clinically stable and started on EEEF and 119 (40 %) babies completed EEEF. These babies had 96% survival rate that could be due to the higher use of human milk in their unit.

Late introduction of enteral feeds

Various observational studies have shown that delaying the initiation of enteral feeding about 5– 7 days after birth and increasing the volume of enteral feeds slowly (<24 ml/Kg/ day) is linked with a lesser risk of developing necrotizing enterocolitis.

Late initiation of feeds leads to villous atrophy, decreased hormone and enzyme production and delayed functional maturation of the GI tract and results in abnormal microbial colonisation [20]. This may ultimately lead the gut at risk for NEC [21] and longer duration of hospital stay. All these factors leads to prolonged use of parenteral nutrition which results in increased risks of late onset sepsis, cholestatic jaundice [22] and vitamin and mineral deficiencies.

Delayed versus Early Introduction of progressive enteral feeds

Cochrane review 2013 including seven RCTs with 964 babies concluded that there was no difference in the incidence of NEC between early (up to 4 days after birth) or late (later than 5-7 days after birth) introduction of progressive enteral feeds for preterm, VLBW babies[23]. Sub group analysis of these trials also concluded that there was no statistically significant effect on the risk of NEC even in growth-restricted infants with abnormal umbilical artery Doppler flow [24].

Slow versus faster advancement of enteral feed volumes

The Cochrane review 2013 of five randomised controlled trials with 588 infants comparing slow advancement (defined as 15–20 ml/Kg/day) and faster advancement (30–35 ml/Kg/day) concluded that no statistically significant increase in incidence of NEC among both the

groups[25]. The babies in slow advancement group took longer time to regain birth weight (median difference 2-6 days) and to establish full enteral feeds.

Standard feeding practices

Six studies (1978-2003) were analysed the incidence of stage II and III NEC in preterm, LBW neonates. Considerable heterogeneity including variation in the feeding practices were identified before and after implementation of a standard feeding regimen. A systematic review by Patole et al [26] indicated that any standard feeding regimen results in a 29% (95% CI 3% to 48%) decrease in the risk of NEC.

The reasons could be standard feeding regimen increases the awareness of clinician regarding present evidence of feeding policies, changing from formula to breast milk and early detection of NEC by implementing evidence based written feeding protocols.

Feeding in IUGR babies

Growth restricted infants are at increased risk of developing NEC[27] and enteral feeding introduction was frequently delayed.

In ADEPT trial[28] 400 babies, GA< 35 weeks with abnormal antenatal umbilical artery Doppler study allocated to an "early" or "late"

enteral feeding groups starting milk feeds on day 2 and day 6 after birth, respectively and feeds increased gradually. In early group full feeds were achieved at an 18 days compared with 21 days in the late group. No difference was found in the incidence of NEC, particularly for serious Bell's stage 2 or 3 and rates of all-stage NEC was 18% in the early group and 15% in the late group.

Speed of Increasing Feeds Trial (SIFT)

SIFT is a randomised controlled trial will enroll 2500 very preterm or VLBW infants. The trial will compare advancing enteral feeds at either 30 ml/Kg/day or 18 ml/Kg/day. Both human milk-fed and formula-fed infants will be eligible to participate. The primary outcome is death or moderate or severe disability at 2 years.

Beneficial effects of breast milk

Human milk empties from the stomach faster than formulas, so feedings can be advanced more easily, reach full feedings faster and need less intravenous fluids. Human milk fed infants spend fewer days in the hospital, less necrotizing enterocolitis, retinopathy of prematurity[29] and sepsis. Anti infective properties of breast milk is due to the presence of higher amount of IgA, lysozyme and lactoferrin and various immunomodulatory factors [30, 31]. Non- pathogenic bacteria from mother

transmitted via breast milk promotes enteromammary immune responses[32]. Breast fed babies tend to have improved cognitive skills and behavior ratings.

Feeding human milk improve feed tolerance in preterm VLBW neonates. Schanler et al [33] in his study found that babies receiving at least 50ml/Kg/day of human milk had decreased number of feed intolerance and reached full enteral feeds rapidly. Paula M. was able to show in neonates weighing ≤1250 grams, enteral feeding with minimum 50% maternal milk was associated with fewer days to full enteral feeding. The above studies emphasize the importance of breast milk in reducing feed intolerance.

Human milk benefits in preterm infants

The long chain polyunsaturated fatty acids (LC-PUFA) like arachidonic acid and docosahexaenoic acid in breast milk improve the long term neurodevelopment outcomes. Since the accretion of LC-PUFA occurs during the third trimester, preterm babies are deficient in LC-PUFA and are prone for neurodevelopmental impairment. Hence early enteral feeding in premature infants is associated with better neurological outcome.

Cholesterol is an important component of myelin membranes [34] and in the postnatal period increase in synapse number requires large amounts of cholesterol. Breast milk has significantly higher quantities of cholesterol compared to formula feeds [35]. Hence breast milk plays an important role in white matter development and cognition, through enhanced glial production/myelination [34].

The practical difficulty of initiation of full enteral feeds is the adequacy of breast milk during the initial few days. Hence lactational encouragement and support for the mother is most important. The alternative is the use of donor breast milk which is the next best to biological mother's milk (WHO) from human milk banks.

Donor milk

The first human milk bank opened in Vienna, Austria, in 1909. At present 517 human milk banks are present all over the world. Asia's first human milk bank was opened at Sion Hospital Mumbai on 27 Nov. 1989 under the guidance of Dr Armeida Fernandez there are 25 breast milk banks in our country at present.

In a recent meta-analysis by Boyd et al[36] reported that donor milk decreases the risk of NEC by about 79%. In 1984, Narayanan et al [37] showed pasteurized human milk gives protection against infection where

as when formula was added to pasteurized milk infection rate was increased.

Clinical studies comparing donor milk and formula

In a recent systematic review Boyd et al compared formula and donor milk feeding of VLBW babies. Formula fed babies had increased rates of weight gain, linear growth and head growth in short term where as there was no difference on long-term growth rates and neurodevelopmental outcomes. The study also confirmed that formula fed babies had 4-fold increased risk of NEC[36].

Schanler RJ [33] in a randomized controlled trial found that when mother's own milk was supplemented either with preterm formula or donor milk the rate of late onset sepsis was similar between both the groups.

The nutritional content of donor milk

There is no standardization of the macronutrient and mineral content of the donor milk. Some trials showed significant variation in macronutrient content in donor milk mainly due to natural biologic variability. Some concern exists regarding the effects of heat treatment, particularly for proteins.

Nutritional components like Carbohydrates, fats, fat-soluble vitamins and salts are unaffected or only minimally reduced through the process of pasteurization whereas thirteen per cent of the protein content is denatured.

Table 1: Various components of human milk after freezing and pasteurisation [38]

Component	**Level after freezing and pasteurisation**
IgA	67-100%
IgM	0
IgG	66-70%
Lactoferrin	27-43%
Lysozyme	75%
Lipases	0
Monoglycerides and Free fatty acids	100%

STUDY JUSTIFICATION

The initiation and rate of progression of enteral feeds in preterm VLBW neonates is an area of clinical ambiguity. Enteral nutrition has been postponed due to fear of feed intolerance and the threat of necrotizing enterocolitis. Significant proportions of the babies acquire extra uterine growth restriction (EUGR). Thus, efforts should be focused on improving the early nutrition of these babies, allowing them to reach satisfactory growth rate. Optimizing feeding in this group of babies has short term and long-term health implications. Early enteral feeding and rapid advancement of feeding have shown to be beneficial in not only AGA babies but also in SGA, IUGR babies with abnormal umbilical artery Doppler study. It is also recommended by various systemic reviews and Meta analysis. Standardized feeding guidelines for VLBW neonates are lacking in the literature and heterogencity of feeding practices among various neonatal units' results in difference in growth and various feed related issues. Some of these feeding practices are not based on evidence but based more on personal experiences or unit culture.

This study was designed to compare the efficacy of full enteral feeds from day one of life in effecting early regain of birth weight compared to standard feeding in hemodynamically stable VLBW neonates.

Research Question:

Does initiation of full enteral feeding with human milk from day one of life more effective than standard feed in regaining of birth weight in hemodynamically stable VLBW babies weighing between 1000-1500 grams?

HYPOTHESIS AND OBJECTIVES

Hypothesis:

In hemodynamically stable VLBW neonates weighing between 1000-1500 grams initiation of full enteral feeding with human milk from day one of life would be associated with rapid regain of birth weight when compared with infants receiving feeds according to the standard protocol.

OBJECTIVES:

Primary objective:

To evaluate the effects of full enteral feed (60 ml/Kg/day of human milk on day one, 20ml/Kg/day during feeding advancement) started from day one of life (intervention) in enhancing the regain of birth weight compared to that of standard feed (both human milk feeds and intravenous fluid) in a group of hemodynamically stable VLBW babies with normal antenatal Doppler study.

OUTCOME OF THE STUDY

Primary Outcome :

Number of days taken to regain the birth weight in hemodynamically stable VLBW neonates receiving full enteral feeding from day one of life compared to neonates receiving standard feeds.

Secondary outcomes:

To compare the following clinical outcome in the two groups

1. Duration of hospital stay.
2. Incidence of Necrotising Enterocolitis (NEC)
3. Incidence of sepsis,
4. Need for intravenous fluid therapy.

METHODOLOGY

Study title: Does full enteral feed from day one of life influence weight gain in hemodynamically stable VLBW babies weighing between 1000-1500 grams as against standard feeding?

Study Design: Open labeled randomized control trial

Study centres: Department of Neonatology, Institute of Child Health (out born unit) and Institute of Obstetrics and Gynecology (inborn unit) of Madras Medical College, Chennai, Tamil Nadu, India.

Duration of the Study: December 2013 to March 2014

Materials & Methods:

Subjects:

Hemodynamically stable VLBW Neonates admitted to the newborn wards of the Institute of Child Health, Institute of Obstetrics & Gynecology, Egmore, Chennai.

Inclusion Criteria:

- Haemodynamically stable VLBW neonates weighing between 1000 gms-1500gms.
- Admission within 24 hrs of birth into the unit.

Exclusion Criteria:

- Major congenital malformation.
- IUGR with abnormal antenatal Doppler.
- Hypoglycemia requiring IVF therapy.
- Need for intra-uterine transfusion.

Sample Size:

Sample size was calculated with the hypothesis that starting VLBW babies on full enteral feeding with human milk was associated with shorter duration to regain birth weight. It was assumed that full enteral feed babies regained the birth weight in 12 days with standard deviation of 2.5 days and standard feed babies regained the birth weight in 14 days with standard deviation of 3 days with the significance level of 5%($\alpha = 0.05$) and the power of 80%($\beta = 0.2$), the required sample size for two sided is 30 in each group. We enrolled 69 babies in the study after randomization.

Recruitment and randomization:

Informed written consent for the trial was obtained within the first 24 hours of birth from the parents or care givers. The parents were given verbal explanation about the relevance of the study, benefits and the possible adverse effects by the recruiting clinician. The information sheet was printed in both Tamil and English. After getting consent the babies were randomized and enrolled for the study.

Neonates satisfying the inclusion criteria were randomly allocated to receive feed under any of the two protocols - full enteral feeding group or standard feeding group as per the randomization sequence obtained after opening the sealed envelope. The computer generated randomization sequences with blocks of varying size were inside the envelopes to which the investigator was blinded.

Intervention:

After getting written consent for the trial, babies were randomized and enrolled within 24 hours of birth. Consent was also obtained for use of the donor human milk which was processed. Donor health, history for life style risks and blood screening tests were all assessed similar to a blood donor. Donors were educated regarding the hygienic methods in which milk expression and collection had to be done. Both hand

expression and electrical milk bumps were used for milk expression. Expressed breast milk collected from donors was pooled into sterile 150 ml stainless steel vessels. It was pasteurized (This pasteurization method, known as flash-heat method involves heating milk in a water bath and holding it for 30 minutes at 62°C) and rapidly freezed to -17 degree and stored. During collection an aliquot of pooled milk was removed from each batch and separately poured into a small container and this milk was also pasteurized (Pilot bottle). Milk from the pilot container was sent for microbiological testing. The milk was discarded if any bacterial growth was present.

Pasteurized, frozen milk was thawed by keeping the container in lukewarm water. Frozen milk was not thawed at room temperature as this can result in bacterial contamination. Thawed milk was used within 4-6 hrs. Pasteurized donor milks were stored in the freezer after proper labeling with identification number, pasteurization date and milk culture reports.

Pasteurisation

Human milk storage in freezer

Full enteral feeding group (study group)

Babies were started on enteral feeds with human milk at the rate of 60ml/Kg/day from day one, and progressed by increments of 20 ml/Kg/day until maximum enteral feeds of 180 ml/Kg/day was achieved.

Standard feed group (1000-1200 gram)

Babies were started with human milk feeds at the rate of 20ml/Kg/day on day one along with intravenous fluid of 60 ml/Kg/day. (Total fluid 80ml/Kg/day) Enteral feeds were increased by increments of 20 ml/Kg/day until maximum enteral feeds of 180 ml/Kg/day was achieved.

Standard feed group (1200-1500gms)

Babies were started on human milk feeds at the rate of 40ml/Kg/day along with intravenous fluids 40 ml/Kg/day from day one and human milk feeds were increased by 20 ml/Kg/day until maximum enteral feeds of 180 ml/Kg/day was achieved.

All the babies were fed with human milk only (either mother's own milk or pasteurized donor milk if mother's own milk was not available).

Gastric residual

When gastric aspirate volume was 2-3 ml or less and the clinical condition of the baby is stable, enteral feeds were continued. If the volume of gastric aspirate was 30-50% of pre feed volume and/ or 3 ml/Kg, then the volume of human milk feed was not increased over the following 24 hours.

Indications for withholding feed (two or more of the following)

If the volume of gastric aspriates was above 50% of feed volume,

Increase in abdominal girth measured at the umbilicus by 2 cm or more from baseline in 6 hours interval,

Visible dilated bowel loops or significant emesis,

Minimal blood tinged or coffee ground aspirate.

Episode of NEC (VLBW babies who had clinical symptoms of necrotising enterocolitis (NEC), i.e., at least two of the following signs: vomiting, abdominal distention, pre-feeding residuals, redness of flanks, persistent microscopic or gross blood in stools; and at least one of the following criteria: pneumoperitoneum, pneumatosis intestinalis, unchanging 'rigid' loops of small bowel), duration of hospital stay, number of days on IVFs, incidence of sepsis defined as in an infant

having clinical picture suggestive of septicemia, pneumonia or meningitis along with either of the following - Isolation of pathogens from blood or CSF or urine or abscess (es) during the study period were monitored.

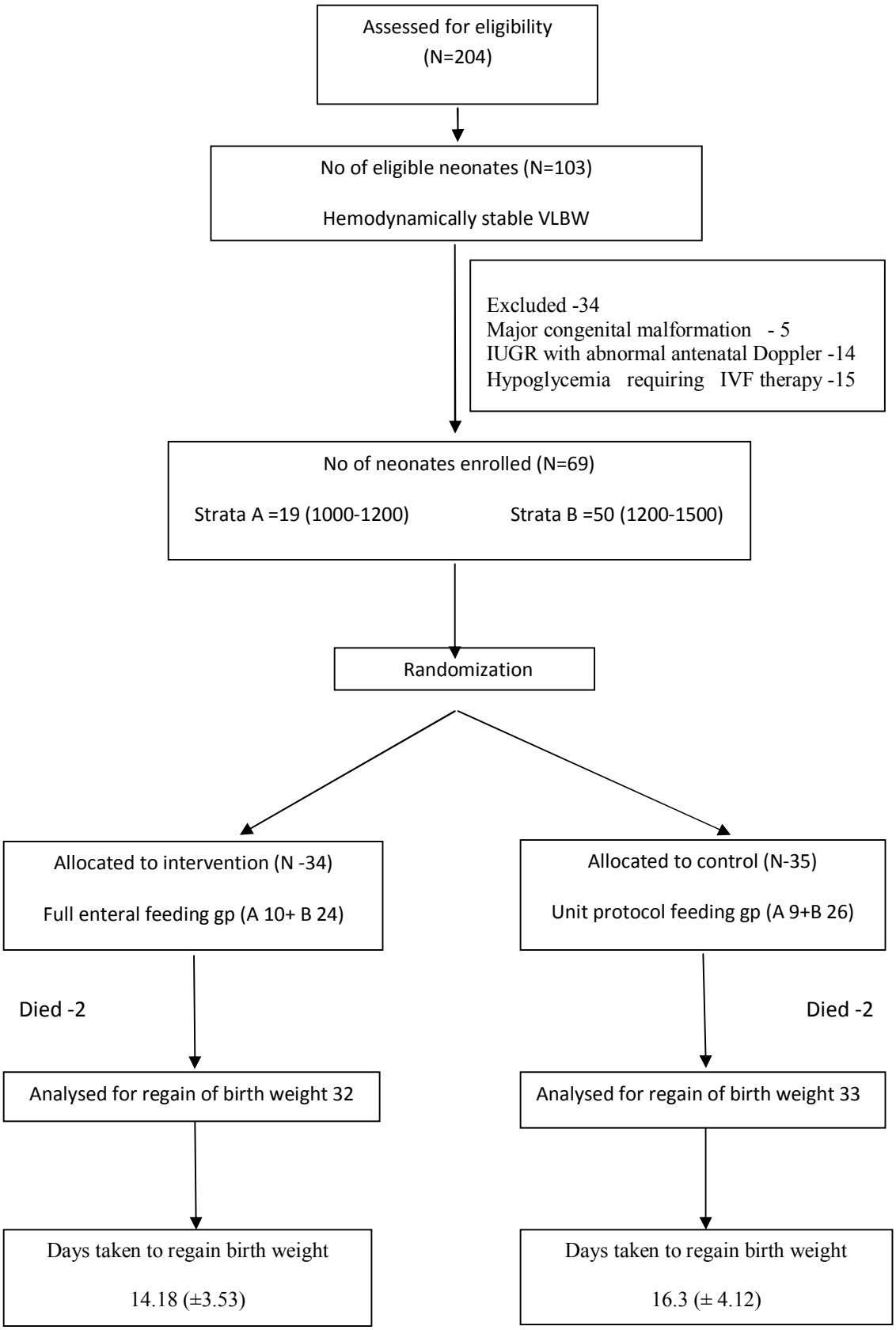
Except for the feeding protocol, other managements in two groups were the same as per unit policy. If any troublesome effect was noted in the study group, then the unit protocol was followed till the time of recovery and the feeds were then started as in the study group. The primary and secondary outcomes of the trial were analysed in intervention and control groups. The risks involved were minimal as mentioned in previous studies. Before giving feed, abdominal girth measurement was done. If there was an increase in abdominal girth above 2 cm, then gastric aspiration was done.

Caregivers were not blinded to the randomized allocation, but the personnel involved in analysis were blinded. Babies were studied during the period of hospitalization and data was collected from the baby's medical chart.

During the study period, the following data were monitored - daily weight measurement, second hourly abdominal girth measurement, gastric aspirates, significant vomiting, apnea, time taken to reach full enteral feedings, feeding details and fluids intake (both intravenous and enteral feed).

Anthropometry (weight, length and head circumference) was recorded at birth. The weight was measured using Neotech electronic weighing scale which can read up to 5 grams. Calibration of the weighing scale was done at regular intervals. Weight was measured daily by trained nurses or doctors. Weight was recorded twice daily until the infant regained birth weight. Length was recorded to an accuracy of 1mm using infantometer weekly and the head circumference was recorded to an accuracy of 1 mm using non stretchable measuring tape weekly. Intrauterine growth status was assessed using the Fenton Growth Chart.

CONSORT FLOW DIAGRAM



RESULTS AND ANALYSIS

204 babies were assessed for eligibility and 103 babies were found to be eligible as per the inclusion criteria. 34 babies were excluded in view of major congenital malformations (5), IUGR with abnormal antenatal Doppler (14) and hypoglycemia requiring IVF therapy (15). We enrolled 69 babies for the study. The enrolled babies were stratified based on birth weight. 19 babies had birth weight between 1000 to 1200gm. 50 babies had birth weight between 1200 to 1500gm . These babies were randomly assigned to the intervention and control groups. Thirty four babies were in the full enteral feeding group (intervention) and thirty five babies were in the standard feeding group (control). 32 babies (2 deaths) in intervention group and 33 babies (2 deaths) in control group were available for analysis of primary outcome.

The data are presented as numbers (percentage) for categorical variables, or means (SD) for normally distributed continuous variables and median (IQR) when the distribution was skewed.

Maternal characteristics

Baseline maternal variables like age, parity, complications and steroid administration were comparable in intervention and control groups

Table : 1 Baseline Maternal Characteristics

Variable	Full enteral feeding n-34 N (%)	Standard feeding n-35 N (%)	P value
Age in years*	24.61 (±4.11)	25.14 (±4.50)	0.61
Primi	21(61.8%)	18(51.4%)	0.46
Anaemia	12 (35.3%)	13(37.1%)	1
Hypertension	12 (35.3%)	14(40%)	0.87
Diabetes mellitus	1 (2.9%)	1(2.9%)	1
Antenatal steroids			
Partial	16 (47.1%)	18 (51.4%)	0.78
Complete	7 (20.6%)	5 (14.3%)	
Infection			
Fever	3(8.8%)	2 (5.7%)	0.84
P PROM	5(14.7%)	8 (22.8%)	
Oligohydramios	3 (8.8%)	2 (5.7%)	0.67

Table : 2 Baseline Neonatal Characteristics

Variable	Full enteral feeding n-34 N (%)	Standard feeding n-35 N (%)	P value
Male	18(52.9 %)	20 (57.1 %)	0.91
Birth weight (gms)*	1290 (±153.7)	1308 (±150.5)	0.63
Gestational age (wks)*	31.4 (±1.8)	31.9 (±2)	0.21
Growth status AGA SGA	 27 (79.4%) 7(20.6%)	 27 (77.2%) 8 (22.8%)	0.72
Mode of delivery Vaginal delivery LSCS	 22 (64.7 %) 12 (35.3%)	 20 (57.1%) 15 (42.1%)	0.69
Apgar< 7 at 5 mts	3(8.8%)	2(5.7%)	0.67
Out born	8 (23.5%)	11 (31.4%)	0.64

*-Mean / SD

The neonatal demographic variables that could affect regain of birth weight were evenly distributed and there was no statistical difference between two groups.

Table : 3 Intervention during study period

Co intervention	Full enteral feeding n-34 N (%)	Standard feeding n-35 N (%)	P value
CPAP days			
< 3 days	10 (29.4%)	12 (34.3%)	
3- 7 days	9 (26.5%)	5 (14.3%)	0.30
>7 days	3 (8.8%)	2 (5.7%)	
Ventilation days			
< 3 days	2(5.9%)	6 (17.1%)	
3- 7 days	7(20.6%)	3 (8.6%)	0.39
>7 days	1(2.9%)	3 (8.5%)	

Babies receiving interventions like CPAP and invasive ventilation were evenly distributed in both the groups.

Table : 4 Mortality

Parameter	Full enteral feeding n -34 N (%)	Unit protocol feeding n -35 N (%)	P value
Mortality	4 (11.8%)	3 (8.6%)	0.710

Four babies died in full enteral feeding group and three babies died in standard feeding group (p - 0.7). Mortality between the two groups is not statistically significant.

Table : 5 Primary outcome

Variable	Full enteral feeding (n -32)	Standard feeding (n - 33)	P value
Days taken to regain birth weight*	14.18 (±3.53)	16.33 (± 4.12)	0.028

*-Mean (SD), Calculated from amongst the babies completing the trial.

Full enteral feeding group regained birth weight at a mean age of 14±3.58 days and standard feeding group at a mean age of 16 ±4.12. Babies regained their birth weight two days earlier in full enteral feeding group than the standard feeding group and this difference was statistically significant (P - 0.028).

Table : 6 Secondary outcomes

Variable	Full enteral feeding (n - 34)	Standard feeding (n - 35)	P value
Duration of hospital stay*	19.76 ±(6.69)	20.71(7.71)	0.58
IVF days**	2 (0-7.75)	6 (5-9)	0.068
Sepsis Clinical sepsis Culture +ve sepsis	 9 (26.5%) 6 (17.64%)	 15 (46.9%) 3 (15%)	 0.29 0.71

*- Mean (SD), **- median (IQR)

Full enteral feeding group infants had lesser days of intravenous fluids compared to babies in the standard feeding group. However, it was not statistically significant. There was no difference in incidence of clinical or culture positive sepsis and duration of hospital stay. None of the babies in our study series developed necrotizing enterocolitis. We used only human milk for feeding in both the groups.

Subgroup analysis:

Two stratified groups were analysed separately. Group A (n-19) (birth weight between 1000 – 1200gms) 10 babies were enrolled in the full enteral feeding group and 9 babies in the standard feeding group

Table : 7 Subgroup analysis for group A: (1000 – 1200gms)

Group A (1000-1200gms) N -19	**Full enteral feeding N -10**	**Standard feeding N-9**	**P Value**
Birth weight	1.08± 71(grams)	1.09±64(grams)	0.87
Gestational age	30±1.7 (weeks)	30±1.87 (weeks)	0.81
Apgar <7 at 5 minutes	2(20%)	1(11.1%)	0.58
SGA AGA	6 4	7 2	0.58
Antenatal steroids Partial course Full course	 5(50%) 2(20%)	 6(66.7%) 1(11.1%)	0.75

Table : 8 Primary outcome (1000-1200 grams)

Parameter	Full enteral feeding N-8	Standard feeding N-7	P value
Days taken to regain birth weight*	17.37(±4.9)	19.8 (±4.3)	0.32

*Mean (SD), Calculated from amongst the babies completing the trial.

Full enteral feeding group regained birth weight at a mean age of 17.37 ± 4.9 days and in the standard feeding group, birth weight was regained at a mean age of 19.8 ±4.3. Babies regained their birth weight two days earlier in full enteral feeding group than standard feeding group and this was not statistically significant.

Table : 9 Secondary outcome (1000-1200gms)

Parameter	Full enteral feeding (n - 10)	Standard feeding (n - 9)	P value
Hospital stay**(days)	22 (15- 28)	27 (22-33)	0.43
Sepsis	2 (20%)	1 (11.1%)	0.76
IVF days**	10 (1.5-17.75)	6 (4.5-16.5)	0.88

*- Mean (SD), **- median (IQR)

Full enteral feeding group had longer duration of intravenous fluids compared to babies in the standard feeding group. However, it is not statistically significant. There was no difference in incidence of clinical and culture positive sepsis, death, duration of hospital stay. None of the babies in our study developed necrotizing enterocolitis.

Subgroup analysis:

Group B 50 babies were enrolled (birth weight 1200 - 1500gms).

24 babies in full enteral feeding group and 26 in standard feeding group

Table : 10 Subgroup analysis (birth weight 1200-1500 gms)

Group B (1200-1500gms) n-50	Full enteral feeding n-24	Standard feeding n-26	P value
Birth weight	1.37±79	1.38±85	0.77
Gestational age	31.87±1.65	32.53±1.86	0.19
SGA AGA	4(16.7%) 20(83.3%)	5(19.2%) 21(80.8%)	0.97
Antenatal steroids Partial course Full course	 11(45.8%) 5(20.8%)	 12(46.2%) 4(15.4%)	 0.86

Tables : 11 Primary outcome (1200-1500gms)

Variable	Full enteral feeding (n - 24)	Standard feeding (n - 26)	P value
Days taken to regain birth weight*	13.12 ±2.17	15.38 ±3.57	0.009

*Mean (SD), Calculated from amongst the babies completing the trial.

Full enteral feeding group regained birth weight at a mean age of 13.12±2.17 days and in standard feeding group at a mean age of 15.38 ± 3.57. Babies regained their birth weight two days earlier in full enteral feeding group than standard feeding group and this was statistically significant (P - 0.009).

Table : 12 Secondary outcome (1200-1500gms)

Parameter	Full enteral feeding (n - 24)	Standard feeding (n - 26)	P value
Hospital stay* (days)	18.62 ±4.08	18.73 ±5.44	0.93
Culture positive sepsis	4 (16.7%)	2 (7.7%)	0.12
IVF days**	1 (0-3.75)	6 (4.75-8.2)	0.003

*- Mean (SD), **- Median (IQR)

Full enteral feeding group babies had lesser number of days of intravenous fluids compared to babies in standard feeding group. It was statistically significant (P - 0.003).

There was no difference in incidence of culture positive sepsis, duration of hospital stay. None of the babies in our study developed necrotizing enterocolitis.

DISCUSSION

Our study compared stable VLBW babies who were fed full enteral feeding from day one using mother's own milk and banked human milk with standard feeding group and has shown that, babies achieved earlier regain of birth weight in full enteral feeding. The full enteral feeding regimen was safe with no differences in the incidence of NEC, sepsis and other feed related morbidities.

Regain of birth weight

Our study has showed that babies in the full enteral feeding group regained their birth weight at 14.18 days and in the standard feeding group at 16.33 days (P - 0.028). This difference was statistically significant. There have been very few published studies evaluating the days required to regain birth weight while on full enteral feeds from day one.

Sanghvi KP et al study [39] found that in babies with birth weight between 1200 -1500 grams, full enteral feed group regained birth weight 7 days earlier than the babies in the control group. In the 1200-1500 grams subgroup analysis in our study, babies regained birth weight at a mean age of 13.1 days in full enteral feeding group and 15.4 days in standard feeding group. The difference was probably because we started

on 60 ml/Kg/day on day one and advanced at a rate of 20 ml/Kg/day where as in their study, the starting volume was 80 ml/Kg/day and the feed advanced at a rate similar to our study. Other reasons could have been the higher incidence of maternal hypertension (36%), poor antenatal steroid coverage (complete course in 20%) and higher proportion of SGA (16%) in our 1200-1500 subgroup babies.

Previous studies have reported that maternal hypertension increased the time taken to achieve full enteral feeds by 11.2%. The reason could be that the abnormality of the umbilical artery blood flow in utero may continue in the splanchnic circulation even after birth for some days compromising feeding tolerance and full enteral feeding attainment [40].

Similarly in Wang et al study [18], early enteral feeding neonates regained their birth weight at 20 days in the 1000 – 1250 grams group. In our study babies in the 1000-1200 grams subgroup regained birth weight by 17 days. This earlier regaining of birth weight in our study could be due to the use of exclusive human milk compared to either breast milk or preterm formula in Wang et al study.

Morgan et al [15] in the meta analysis studied the effects of slow enteral feed advancements (15 to 20 ml/Kg/day) and concluded that

infants in the slow advancement group took more days to regain birth weight (median difference two to six days).

Leaf A [24] et al studied the early and late enteral feeds in preterm (GA 31 wks) SGA babies with abnormal antenatal umbilical artery Doppler waveforms and concluded that babies in the early enteral feed group had better weight score and had lesser days of parenteral nutrition. There was no difference in the incidence of NEC.

Salhotra et al [41] found that babies in the fast enteral feeding group regained birth weight earlier (median 18 days) after their study of Indian infants. They used only expressed breast milk for enteral feeds. Krishnamurthy S [42]et al also concluded that VLBW neonates in the rapid advancement group (30ml/kg/day) regained birth weight earlier (median 16 days vs. 22 days) in their study using expressed human milk or formula.

Our study was comparable with that of an unpublished study done in a tertiary hospital in Mumbai by Joshi et al. In their study, infants in the full enteral feeding group regained birth weight earlier (mean 5.52 days) than those in the standard feed group (mean 12.7). The difference was statistically significant ($p<0.0001$) as in our study. This study enrolled only preterm infants with birth weight 1200 to 1500 grams.

Duration of hospital stay and intravenous fluid

In our trial the number of days of hospital stay was lesser in the full enteral feed group compared to the standard feed group, though it was statistically insignificant (19.76 days in full enteral feeding group and 20.71 days in standard feed group). Similarly, the duration of intravenous fluid administration was lesser in the full enteral feed group compared to the standard feed group though not statistically significant.

In the randomised trial by Caple et al [43] comparing slow and rapid feeding volume progression in preterm infants, it was found that babies in the rapid feed advancement group had lesser intravenous fluid days. The length of hospital stay was lesser in the rapid feed advancement group though it was not statistically significant. Similar results were obtained in the study by Karagol BS et al [44] on comparing slow versus rapid feed advancement in VLBW babies with birth weight 750gms -1250gms.

In Sanghvi KP[39] et al study the number of days in hospital was significantly less in the full enteral feeding group (mean 15.04 days, SD ± 5.26). But in the control group, the mean duration of hospital stay (mean 28.04 days, SD ± 6.76) was relatively high when compared to our sub group babies of 1200-1500 grams birth weight where babies in full

enteral feed and standard feed groups regained birth weight 18.62 days and 18.73 days respectively.

Krishnamurthy S [42] et al, while comparing rapid and slow progression of enteral feeding, found a significantly lesser number of IVF days (median 2 days vs. 3.4 days) ($p < 0.001$), and shorter hospital stay(median 9.5 days vs. 11 days) ($p = 0.003$) in the rapid advancement group using either human milk or formula.

Sepsis

In our study, there was no statistically significant difference in the incidence of infection between the full enteral feed group(17.64%) and standard feed group (15%). The reason could be earlier the use of human milk in both the groups. Lavole et al [44] studied the relationship between early enteral nutrition and CoNS associated late onset bacteremia in VLBW infants. The early nutrition group reached full enteral nutrition earlier and early initiation of enteral nutrition with human milk had reduced the incidence of late onset bacteremia. The next important observation of this study was when enteral nutrition was initiated earlier with formula feed, there was no reduction in the incidence of late onset bacteremia.

Karagol et al [45] while studying on rapid feed advancement found that the incidence of sepsis (culture positive) was less in the rapid feeding group. Hylander et al [46] in his study comparing the presence of infection in human milk feed and formula feeds concluded that human milk feeding had reduced odds of infection.

An unpublished study was done by Chetry et al in New Delhi comparing initiation of total enteral feeds on 1st day of life with standard feeding regimen in VLBW infants. In this study the incidence of culture proven sepsis was higher in the standard feeding regimen group with higher number of days in intravenous fluids with borderline significance (31.8% vs. 15%, p-0.28).

Necrotizing enterocolitis

There was no incidence of NEC in our study. This could be due to the use of exclusive breast milk. Lucas et al[47] found a 6-10 fold increase in necrotizing enterocolitis in babies receiving formula feeds and a 3 fold increase in those who received formula plus breast milk compared to breast milk only. Pasteurized donor milk is similar to raw maternal milk with regards to the risk of NEC.

Leaf A [24] et al conducted a study on initiation of early enteral feeds (within day 2) in Small Gestational age neonates with abnormal umbilical

artery Doppler study. The study concluded that there was no difference in the risk of necrotizing enterocolitis. The Cochrane review by Morgan et al suggested that there was no difference in the risk of NEC between slow and rapid progression of enteral feeds.

Sisk et al[48] wanted to determine if high proportions of (50% or greater) human milk enteral feeding initiated during first 2 weeks of life offered protection against NEC. They concluded that feeding with at least 50% human milk was associated with a six fold reduction in the risk of NEC. This could explain the zero incidence of NEC as both groups in our study group had exclusive breast milk feeding. In the study conducted by Leaf et al[24] in preterm growth restricted infants, there was no difference in the incidence of NEC among those who were fed early or late.

In Sanghvi KP et al[39] study which was done with full enteral feeding from the initial few hours of life, none of the babies developed necrotizing enterocolitis. This was replicated in our study as well.

Boo NY et al[49] studied the risk factor associated with feed intolerance in VLBW babies was due to the delay in starting the first feed and suggested that to promote tolerance, enteral feeds should be started as soon as possible during the first 72 h of life.

The strengths of our study were

- This was a well-designed, randomized control trial with adequate sample size.
- This is one of the few studies done with exclusive breast milk. The breast milk bank in our unit ensured adequate breast milk.
- The strict adherence to feeding policies helped us in comparing the full enteral feeds with standard protocol.

The limitations of our study were:

- The donor milk was not classified as term and pre term milk. Hence a difference in the protein and caloric contents might have had an influence on the outcomes.
- Since different clinicians assessed the feed intolerance and other outcomes, there might have been observer bias.
- Long term neurological outcomes were not studied.

CONCLUSION

Full enteral feeding from day one of life in hemodynamically stable very low birth weight babies with exclusive human milk (both maternal and donor milk) results in fewer days to regain birth weight.

There is also no evidence that full enteral feeding has adverse effects particularly on the risk of necrotizing enterocolitis. We conclude that initiating full enteral feeding practice is an effective, feasible, cost effective and safe intervention.

There is less chance of NEC even in growth restricted babies with this schedule. Hence it would be prudent to commence full enteral feeding from first day of life and prevent inadequate nutrition in this critical period of growth.

IMPLICATIONS FOR PRACTICE:

1. Full enteral feeding can be initiated from day one in hemodynamically stable VLBW neonates safely with careful monitoring.
2. Full enteral feeding with standardized feeding guidelines minimizes the feed related morbidities.

3. The practice of full enteral feeding from day one would provide an encouragement for exclusive breast feeding policy among the care givers and the mothers.
4. A donor breast milk bank with preterm and term milk will be of more use.

IMPLICATIONS FOR FURTHER RESEARCH:

A larger randomized controlled trial with more number of babies would provide us with a better knowledge of the secondary outcomes like duration of hospital stay and incidence of sepsis.

The donor milk diet may be a variable in terms of caloric and protein content and the nutritional components of donor milk may be altered by pasteurization. Hence a study analyzing the nutrient contents of the donor milk would be of more use. Further studies with fortified donor human milk would also provide us additional information.

A long term follow up study analyzing the growth and neurodevelopmental outcome would provide us the impetus to use breast milk from day one of life.

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ANNEXURE I

STUDY PROFORMA

Name: B/O Gender: M/F IP No :

Address: Study No :

Hospital : ICH / IOG

Phone No:

Date of birth : Gestational age :----Weeks----days

Date of admission : Date of recruitment :

Birth weight : ---------grams Growth Status : SGA/AGA/LGA

Mode of delivery : Labor Natural /Instrumental /LSCS APGAR :

Resuscitation details :

Maternal details

Name : Age : Gravid status :

LMP : EDD :

Antenatal steroid : Full course/ Partial course/ No steroids

Abnormal fetal doppler : Yes/No Anemia : Yes/No

PIH/ Preeclampsia : Yes/No Diabetes : Yes/No

Placenta abruption : Yes/No Placenta previa : Yes/No

PROM : ---------hours Maternal fever : Yes/No

Foul smelling liquor : Yes/No

No of PV exam :

Dysuria : Yes/No Meconium Stained Amniotic fluid : Yes/No

Day of life	**Full enteral feeding group**		**Standard feeding group**	
	Milk(ml/kg)	**IVF(ml/kg)**	**Milk(ml/kg)**	**IVF(ml/kg)**
Day 1(0-24hrs)				
Day 2(24-48hrs)				
Day 3(48-72hrs)				
Day 4(72-96hrs)				
Day 5(96-120hrs)				
Day 6(120 - 144hrs)				
Day 7 +(144 hours onwards)				

DAY OF LIFE										
WEIGHT(GMS)										
ENTERAL FEEDS										
TOTAL FLUID VOLUME ml/kg/day										
MOTHER'SMILK										
DONOR MILK										
IVF ml/kg/day										
MEASURES OF FEED INTOLERANCE GASTRIC ASPIRATE >50% (Y/N) APNOEA,BRADYCARDIA,RESP SIGNS(Y/N) TEMPARATURE INSTABILITY (Y/N) ABDOMINAL										

DISTENSION(Y/N) ABDOMINAL TENDERNESS(Y/N) BRIGHT RED BLOOD/RECTUM(Y/N) ABSENT BOWEL SOUNDS(Y/N) VOMITING(Y/N)										
FEEDS OMITTED(Y/N)										
FEEDS REDUCED/NOT INCREASED(Y/N)										
STOOLS PASSED(Y/N)										
ABDOMINAL RADIOLOGY NORMAL XRAY(Y/N) INTESTINAL DILATATION(Y/N) PEUMATOSIS INTESTINALIS/PORTAL VENOUS GAS PNUMOPERITONEUM(Y/N)										

ANNEXURE II

PATIENT INFORMATION SHEET

Postnatal growth failure is a problem in very-low-birth weight infants. This subnormal growth often persists into early childhood. Early nutrition and neuro developmental outcome are linked. Breast milk is the standard of care for VLBW infants. we can improve outcomes by preventing "nutritional insults" during the a critical period between birth and when birth weight is regained when optimal nutrition has its greatest benefit.

Hence we are conducting a study by using pasteurised, caloric human milk and time taken to regain birth weight in very low birth weight infants admitted in our newborn unit .

After obtaining your consent your baby will be included in our trial. In this study one group of babies will be initiated on full enteral feeds on Day 1 with pasteurized human milk from the Breast Milk Bank in our institute. The babies in the other group will be fed as per the unit protocol. Your baby will be enrolled in either of the two groups randomly.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of the investigator signature of the parent

Date ;

Place : Chennai

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு
செறிவூட்டப்பட்ட தாய்ப்பாலைக் குறைமாத குழந்தைகளுக்கு அளிக்கும் ஆய்வு.

பெயர் :
வயது :
பால் :

தேதி :
உள்நோயாளி எண் :
ஆராய்ச்சி சேர்க்கை எண் :

மிகவும் எடை குறைவாகப் பிறக்கும் குழந்தையின் ஆரம்பகால வளர்ச்சி, அக்குழந்தையின் ஆரோக்கியத்திற்கு அடித்தளமாக அமைகிறது. இக்குழந்தைகளின் வளர்ச்சியில் தாய்ப்பாலின் முக்கியத்துவத்தையும், பிற்கால மூளை வளர்ச்சியில் தாய்ப்பாலின் பங்களிப்பையும் சமீபத்திய ஆய்வு முடிவுகள் உறுதி செய்கின்றன.

செறிவூட்டப்பட்ட தாய்ப்பாலை குழந்தைகளுக்கு அளிக்கும் ஆய்வு, பச்சிளம் குழந்தைகள் பிரிவு, எழும்பூர் குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி மையம் மற்றும் பச்சிளம் குழந்தைகள் பிரிவு, மகப்பேறு மற்றும் பெண்கள் நோயியல் மையத்தில் நடைபெறுகிறது.

இந்த ஆய்வில், கலந்து கொள்ள உங்கள் குழந்தை தகுதி உள்ளதாக இருந்தால், உங்கள் விருப்பத்தின்படி நீங்கள் சம்மதிக்கலாம்.

உங்கள் குழந்தை பரிசோதனைப் பிரிவில் வகைப்படுத்தப்பட்டால், எடை குறைவான குழந்தைகளுக்குத் தேவையான, செறிவூட்டப்பட்ட தாய்ப்பால், வங்கியில் இருந்த பெறப்பட்டு குழந்தைக்குத் தரப்படும். குழந்தையின் எடை தினமும் எடுக்கப்பட்டு, குழந்தையின் வளர்ச்சி கண்காணிக்கப்படும்.

நீங்கள் இந்த ஆய்விலிருந்து விலக நினைத்தால் தாராளமாக விலகலாம். உங்களின் இந்த முடிவானது மருத்துவ சிகிச்சையில் எந்தவித பாதிப்பையும் ஏற்படுத்தாது என்று உறுதி அளிக்கிறோம்.

இந்த ஆய்வின் முடிவு தங்களுக்கு ஆய்வின் இறுதியில் தெரிவிக்கப்படும். ஆய்வு நிகழும்போது ஏதேனும் மாறுபாடு இருந்தால், குழந்தையின் சிகிச்சைக்கு உதவும் பொருட்டு முடிவுகள் உங்களுக்குத் தெரிவிக்கப்படும்.

ஆய்வாளரின் கையொப்பம் :
பெயர் :
நாள் :

பெற்றோர்/பாதுகாப்பாளர் கையொப்பம் :
பெயர் :
நாள் :

ANNEXURE III

CONSENT FORM

I Ms/Mr._____ M/O//F/O, B/O _____Sex_____ Hosp. No._____ admitted in the Neonatal unit was explained by the doctor that my baby is a very low birth weight baby at birth and I understood the nutritional needs of my baby. I am willing to participate in this trial and I gave my consent to use pasteurised donor human milk to my baby. The adverse effect like feed intolerance were explained to me.

The doctors have explained to me the nature and the purpose of the trial. I have given my consent only after completely understanding the details that were explained to me. I understand that my baby's routine clinical management is not affected by my participation in this trial.

I have given this consent to be enrolled in this study with my full consciousness. I am willing for my baby to be enrolled in this study without any ones compulsion and I am fully aware that I can withdraw from the trial at any time during the study.

Signature of Investigator Signature of the parent

Date;

Chennai -8.

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :
செறிவூட்டப்பட்ட தாய்ப்பாலைக் குறைமாதக் குழந்தைகளுக்கு அளிக்கும் ஆய்வு.

பெயர் :
வயது :
பால் :

தேதி :
உள்நோயாளி எண் :
ஆராய்ச்சி சேர்க்கை எண் :

நான் மருத்துவரின் மூலம் மிகவும் குறைவான எடையுடன் பிறக்கும் குழந்தைகளுக்குத் தாய்ப்பாலின் நன்மைகளையும், அவசியத்தையும் தெரிந்து கொண்டேன்.

மருத்துவரின் வாயிலாக மிகவும் எடை குறைவான குழந்தைகளுக்குத் தேவையான வங்கியில் இருந்து கிடைக்கும் செறிவூட்டப்பட்ட தாய்ப்பாலின் பயன்களை அறிந்து கொண்டேன்.

என் குழந்தை ஆய்வின்படி பரிசோதனைப் பகுதியில் வகைப்படுத்தப்பட்டால், செறிவூட்டப்பட்ட தாய்ப்பாலை என் குழந்தைக்கு வழங்க நான் முழுமனதுடன் சம்மதிக்கிறேன். இந்த ஆய்வின் இருபிரிவுகளில், எந்தப் பிரிவிலும் என் குழந்தை வரலாம் என்பதையும் நான் அறிவேன்.

மருத்துவர் இந்த ஆராய்ச்சி குறித்த விளக்கங்களை எனக்குக் கூறியுள்ளார். ஆராய்ச்சி தகவல்தாளை நான் பெற்றுக் கொண்டேன்.

நான் இந்த ஆய்வில் எவரின் கட்டாயத்தின் பேரிலும் கலந்து கொள்ளவில்லை. ஆய்வில் ஏற்படக்கூடிய விளைவுகளையும் மருத்துவர் எனக்கு தெளிவுபடுத்தியுள்ளார்.

ஆய்வின் எந்தவொரு நிலையிலும் ஆய்விலிருந்து விலகும் முழு உரிமை எனக்கு உண்டு என்பதை நான் அறிவேன். நான் என்னுடைய முழு சுதந்திரத்துடன் இந்த ஆய்வில் கலந்து கொள்ள சம்மதிக்கிறேன்.

ஆய்வாளரின் கையொப்பம் :
பெயர் :
நாள் :

பெற்றோர்/பாதுகாப்பாளர் கையொப்பம் :
பெயர் :
நாள் :

S.No	R.No	Feeding Type	Name	Sex	INST	APGAR		GA	BW	Growth	Anemia	MOD	Hypertension	GDM	ANS	Infection	Abn Doppler	Oligohydraminos	Feed Intolerance	Hypoglycemia	Comorbid	Sepsis	CPAP	Ventilation	IVF days	No. of days to suck feeds	Days taken to regain Birth Weight	duration of hospital stay	HC on admission	Rate of increase HC/Wk	Length on Admission	NEC	Death
1	A 25	1	B/o Noorjahan	1	1	3	3	31	1060	2	2	2	2	2	1	1	2	2	2	2	3	1	2	1	0	13	17	23	26	0.65	40	2	2
4	A 10	1	B/o Dhanalakshmi	2	2	3	3	30	1160	2	2	2	2	2	3	6	2	2	1	1	1	2	3	3	17	24	23	33	25.5	0.35	39	2	2
3	A 12	2	B/o Lakshmi	2	1	3	3	32	1100	2	1	1	2	2	3	1	2	2	1	2	1	2	1	1	21	29	28	42	25	0.45	37	2	2
19	A 11	1	B/o Ramesa	2	2	3	3	31	1190	2	1	1	2	2	3	2	2	2	2	1	1	3	2	3	6	0	0	6	26	0	37	2	1
5	A 19	2	B/o Meharaj	1	2	3	3	29	1050	2	2	2	1	2	3	1	2	2	2	1	3	2	2	2	8	16	23	35	23.5	0.4	36	2	2
9	A 21	1	B/o Parameshwari	2	1	3	3	32	1050	2	2	2	1	2	3	1	2	2	2	2	3	1	1	1	0	8	10	11	26.5	0.65	37	2	2
7	A 23	2	B/o Anusiya	2	1	3	3	28	1000	2	2	1	2	2	3	1	2	2	2	2	2	2	1	1	6	19	17	31	24.5	0.35	37	2	2
10	A 3	1	B/o Maliga	2	2	2	3	28	1200	2	2	1	2	2	1	6	2	2	1	2	7	2	3	1	14	22	20	27	24.5	0.45	36	2	2
6	A 5	1	B/o Kaliyammal	2	2	3	3	31	1030	1	1	1	2	2	2	1	2	1	2	2	1	2	3	1	6	18	16	23	26	0.5	37	2	2
8	A 8	1	B/o Karpagam	1	2	2	3	28	1030	2	1	1	1	2	3	1	2	2	1	1	2	3	3	4	20	0	0	21	23.5	0	35	2	1
24	1 B	1	B/o Geetha	1	2	3	3	30	1350	2	1	1	1	2	3	1	2	2	1	2	3	1	2	1	1	10	15	19	28	0.5	40	2	2
12	A 4	2	B/o Gunasundari	2	1	3	3	28	1100	2	2	2	1	2	3	1	2	1	1	1	8	3	2	3	20	0	0	20	23.5	0.3	34	2	1
59	11 B	1	B/o Geetha	1	1	3	3	30	1350	2	2	1	1	2	3	6	2	2	2	2	3	1	2	1	2	14	16	21	25.5	0.35	41	2	2
14	A 13	2	B/o Thiruparasundari	1	2	3	3	33	1000	1	1	2	2	2	2	6	2	1	1	2	1	1	1	1	13	18	19	27	25	0.5	37	2	2
15	A 9	2	B/o Sandhiya	1	2	3	3	29	1120	2	2	1	2	2	3	6	2	2	1	1	2	1	1	1	6	17	19	28	27	0.5	38	2	2
16	A 28	2	B/o Mumtaj	1	2	3	3	31	1155	2	2	1	2	2	3	6	2	2	1	2	9	2	1	2	4	0	0	4	26.5	0.2	37	2	1
17	A 18	2	B/o Lalitha	2	1	3	3	31	1170	2	2	1	1	2	1	2	2	2	2	2	2	1	1	1	5	16	18	26	28	0.55	38	2	2
18	A 2	2	B/o Rekha	1	2	2	3	32	1150	1	1	2	1	2	1	1	2	2	2	2	2	1	1	1	4	10	15	25	26	0.4	37	2	2
63	17 B	1	B/o Anitha	1	1	3	3	31	1250	2	2	1	1	2	1	1	2	2	2	2	1	1	1	1	0	15	18	22	25.5	0.45	42	2	2
20	20 B	2	B/o Divya Bharathi	1	2	3	3	32	1450	2	2	2	1	2	3	1	2	2	1	2	1	2	3	1	10	14	15	19	27	0.6	39	2	2
66	18 B	1	B/o Mouli	1	2	3	3	33	1440	1	2	2	1	2	1	1	2	2	2	1	3	1	3	1	8	15	14	16	26	0.5	40	2	2
22	46B	2	B/o Sheerin-I	1	2	3	3	30	1340	2	1	1	1	2	3	1	2	2	2	1	7	2	3	4	13	20	22	24	28	0.35	42	2	2

46	2 B	1	B/o Sridevi	2	2	3	3	32	1390	2	2	2	1	2	3	1	2	2	2	2	1	1	2	1	0	13	15	21	25.5	0.35	38	2	2
43	21 B	1	B/o Sarala	2	2	3	3	33	1490	2	1	1	1	2	3	1	2	2	2	2	1	1	1	1	0	6	13	17	27.5	0.4	38	2	2
25	4 B	2	B/o Mangaiyakarasi	1	2	3	3	33	1450	2	2	2	2	2	1	1	2	2	2	1	7	3	2	3	14	16	21	23	27	0.4	43	2	2
26	27 B	1	B/o Karpagam-I	1	2	3	3	31	1320	2	1	2	2	2	2	1	2	2	2	2	3	1	1	1	0	12	16	23	27.5	0.35	40	2	2
27	56 B	2	B/o Karpagam-II	2	2	3	3	31	1500	2	2	2	2	2	2	1	2	2	2	1	1	2	2	2	6	10	16	23	29	0.45	43	2	2
44	32 B	1	B/o Dhanalakshmi	1	2	3	3	31	1400	2	2	1	1	1	3	1	2	2	2	2	1	1	1	1	2	13	15	18	28	0.55	42	2	2
29	30 B	2	B/o Iswariya	1	2	3	3	35	1480	1	1	1	2	2	3	1	2	2	2	2	1	1	2	1	4	7	11	13	29	0.35	41	2	2
30	5B	2	B/o Kavitha-II	1	2	3	3	32	1400	2	1	1	2	2	1	1	2	2	2	2	1	2	2	1	10	12	18	23	27.5	0.35	42	2	2
31	72 B	2	B/o Thenmozhi	2	2	3	3	35	1390	5	2	1	1	2	3	1	2	2	2	2	1	1	1	1	4	3	10	12	30.5	0.25	43	2	2
65	33 B	1	B/o Chitra	2	2	3	3	33	1485	1	2	2	2	2	3	2	2	2	2	2	2	3	2	2	10	16	15	18	26	0.5	41	2	2
33	71 B	2	B/o Maibeen	2	2	3	3	34	1420	1	1	1	1	2	2	1	2	2	2	1	1	1	1	1	4	6	14	15	28.5	0.45	40	2	2
34	3 B	2	B/o Lakshmi	1	2	3	3	31	1360	2	2	1	1	2	2	2	2	2	2	1	1	1	1	1	7	12	13	15	26.5	0.4	38	2	2
37	37 B	1	B/o Ammu-II(Tri)	2	2	3	3	36	1275	5	2	2	1	2	2	1	2	2	2	2	1	1	1	1	0	5	13	17	27.5	0.65	39	2	2
36	50 B	2	B/o Sofiya Mary	1	2	3	3	31	1230	2	1	2	1	2	3	1	2	2	2	2	3	1	3	1	8	15	10	17	26	0.5	37	2	2
40	41 B	1	B/o Subbulakshmi	2	2	3	3	30	1315	2	2	1	1	2	3	1	2	2	1	1	3	3	2	3	10	22	16	30	26.5	0.35	38.5	2	2
38	24 B	2	B/o Ammu-III(Tri)	2	2	3	3	36	1365	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	5	8	10	17	24	0.5	39	2	2
39	14 B	2	B/o Geetha	2	1	2	3	31	1290	2	1	1	1	2	1	2	1	2	1	2	7	2	3	2	10	15	18	27	26	0.3	36	2	2
56	44 B	1	B/o Suguna-I	2	2	3	3	33	1470	2	2	1	1	2	3	2	2	2	2	2	1	1	1	1	0	5	13	17	26	0.4	36	2	2
28	47 B	1	B/o Tulasi	1	2	3	3	32	1420	2	2	1	2	2	2	1	2	2	2	2	1	1	1	1	0	6	14	16	29	0.7	40	2	2
42	10 B	2	B/o Kavitha	1	2	3	3	32	1350	2	2	2	2	2	3	1	1	2	2	2	3	1	3	1	7	13	13	15	26.5	0.25	38	2	2
62	48 B	1	B/o Vimala	1	2	3	3	29	1250	2	2	1	1	2	1	1	2	2	1	2	8	3	2	3	15	16	15	19	25	0.45	36	2	2
57	51 B	1	B/o Maheswari	2	2	3	3	33	1365	2	2	2	1	2	1	1	2	2	2	2	1	1	1	1	0	6	9	11	26.5	0.55	40	2	2
45	57 B	1	B/o Mala-I	1	2	3	3	33	1460	1	2	1	1	2	1	1	2	2	2	2	1	2	2	1	0	6	17	16	30.5	0.45	43	2	2
32	6 B	1	B/o Usha	2	2	3	3	33	1500	2	1	2	2	2	1	1	2	2	2	2	1	1	1	1	0	5	15	18	30	0.35	42	2	2
47	42 B	2	B/o Anuradha	1	1	3	3	33	1410	2	1	2	1	2	3	1	2	2	2	2	1	1	1	1	5	7	10	11	27.5	0.35	40	2	2
48	60 B	2	B/o Shalini-I	2	1	3	3	32	1350	2	1	2	2	2	3	6	2	2	1	2	3	2	1	1	9	16	15	18	28.5	0.25	40	2	2
49	34 B	2	B/o Easwari	1	2	3	3	33	142	2	2	1	1	2	3	1	2	2	2	2	3	2	2	1	4	6	10	10	28	0.5	39	2	2

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50	68 B	2	B/o Punitha	1	2	3	3	35	1495	1	2	1	1	2	1	1	2	2	1	1	1	1	1	1	3	5	9	9	26	0.5	40	2	2
51	45 B	2	B/o Shalini-II	1	2	3	3	35	1450	2	2	1	1	2	1	1	2	2	1	2	1	2	1	1	6	12	14	18	30	0.45	41	2	2
52	38 B	2	B/o Benitha	2	1	3	3	30	1260	2	2	1	1	1	1	1	2	2	1	2	1	3	1	1	8	16	18	23	26	0.4	35	2	2
53	64 B	2	B/o Suguna-II	2	2	3	3	34	1450	2	2	1	1	2	3	1	2	2	2	2	1	2	1	1	3	4	15	17	27	0.6	41	2	2
54	28 B	2	B/o Nishanthini	1	1	3	3	35	1500	1	1	1	1	2	1	6	2	2	1	2	1	1	1	1	4	3	8	13	27.5	0.7	37	2	2
21	61 B	1	B/o Asha	1	2	3	3	33	1420	2	1	1	1	2	3	1	2	2	2	2	1	1	1	1	0	5	14	16	29	0.4	40	2	2
41	65 B	1	B/o Venda	1	2	3	3	33	1400	2	2	1	2	2	2	1	2	2	2	2	1	1	1	1	0	8	14	16	30	0.45	42	2	2
35	69 B	1	B/o Grace	1	2	3	3	31	1350	2	1	2	1	2	3	1	2	2	2	2	3	2	3	1	3	12	12	14	25.5	0.5	37.5	2	2
60	7 B	1	B/o Indhumathi	2	1	3	3	34	1285	1	2	1	1	2	1	6	2	1	1	1	1	3	2	3	22	0	15	24	25.5	0.35	38	2	1
55	70 B	1	B/o Vanisri	2	1	3	3	30	1350	2	1	1	2	2	2	1	2	2	1	2	3	1	3	1	2	15	13	18	26	0.4	37	2	2
58	73 B	1	B/o Rekha	1	2	3	3	31	1250	2	2	1	1	2	1	1	2	1	2	2	1	2	2	1	1	15	10	20	27	0.5	41	2	2
61	12 B	2	B/o Sangmayadhav-II	2	1	3	3	30	1265	2	2	2	1	2	1	1	2	2	1	2	3	2	1	3	23	0	19	23	27	0.3	40	2	1
23	80 B	1	B/o Sheerin-II	1	2	3	3	30	1430	2	1	1	1	2	3	1	2	2	1	1	2	2	3	3	15	22	18	24	27.5	0.45	42	2	2
2	A 1	1	B/o Shanthi	2	1	3	3	30	1100	2	2	1	1	2	1	1	2	2	2	1	2	1	2	1	2	15	11	17	24.5	0.7	36	2	2
64	78 B	2	B/o Nallini	2	2	3	3	30	1300	2	2	1	1	2	3	6	2	2	2	2	3	1	2	1	8	13	15	21	25.5	0.25	39	2	2
13	A 26	1	B/o Lalitha	1	1	2	3	28	1025	2	2	1	2	2	3	1	2	2	1	1	3	2	2	2	16	28	23	43	25.5	0.6	35	2	2
11	A 6	1	B/o Maheswari	1	2	3	3	33	1020	5	1	2	1	2	2	6	2	2	2	2	1	2	3	3	21	0	19	21	26.5	0.2	38	2	1
67	63 B	2	B/o Amudha	2	1	3	3	33	1380	2	2	2	2	2	3	6	2	2	2	2	1	1	2	1	6	7	10	10	26	0.25	37	2	2
68	49 B	2	B/o Kalaiarasi	1	2	3	3	32	1440	2	2	1	2	2	1	1	2	2	2	2	3	2	2	1	6	12	14	15	26.5	0.4	36	2	2
69	B 76	2	B/o Janani	1	2	3	3	31	1200	2	1	2	1	2	1	1	2	2	2	2	2	1	2	1	8	12	17	28	27.5	0.4	38	2	2